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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/143,155	08/28/98	DITULLIO	P 10275/045002

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EXAMINER	
LEE, G	
ART UNIT	**PAPER NUMBER**
1632	5

DATE MAILED: 12/21/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/143,155	DiTullio et al
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-11 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-11 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C.119 (e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,843,705. Although the conflicting claims are not identical, they are not patentably distinct from each other because the applicant claims a transgenically produced antithrombin III and method for producing antithrombin III in mammalian milk, comprising transgenic mammal that expresses a transgene which encodes a human antithrombin III with a monosaccharide composition which includes GalNAc or Fuc, GlcNAc, Gal, Man, NANA/NGNA having one of its glycosylation sites comprising oligomannose and/or hybrid oligosaccharide structures; collecting milk ; and isolating human antithrombin III from milk.

They are not patentably distinct because the claims of the instant application and the claims of U.S. Patent No. 5,843,705 are of overlapping. The instant claims are drawn to transgentically produced human Antithrombin III comprising a monosaccharide composition which comprises GalNAc along with Fuc, GalNAc, Gal, Man and NANA/NGNA (lacks O-linked glycosylation; oligomannose and/or hybrid oligosaccharide structures wherein primarily an oligomannose or hybrid type structure on one site and complex oligosaccharide on the remaining 3 sites; monosaccharide is partially sialylated, wherein includes sialic acid which includes NGNA; fucose on its proximal GlcNAc on each of the sites having complex oligosaccharides) and the method of producing human Antithrombin III in said mammal wherein mammal is a goat. The claims of U.S. Patent No. 5,843,705 are drawn to a glycosylated human antithrombin III, wherein a glycosylated human antithrombin III is made by the method of

isolating the glycosylated human antithrombin III from milk, wherein the milk is collected from a transgenic goat, which goat expressed in mammary tissue a transgenic encoding human antithrombin III and wherein the human antithrombin III is secreted into the milk produced by the transgenic goat; and wherein the glycosylated human antithrombin III has the following properties: monosaccharide glycosylation comprising GalNAc, Fuc, GlcNAc, Gal, Man, and NANA/NGNA; no O-linked glycosylation; oligomannos and/or hybrid oligosaccharide structures; wherein primarily an oligomannoses or hybrid type structure on one site and complex oligosaccharide on the remaining 3 sites; partially sialylated; sialic acid which includes NGNA; and comprising fucose on its proximal GlcNAc on each of the sites having oligosaccharides and a method for producing human antithrombin III in goat milk. While the scope of glycosylated variants, the method steps are identical of antithrombin III, and the specific embodiments of product claimed in U.S. Patent No. 5,843,705 are clearly encompassed by the instant claim language. Thus, it would have been obvious to one of ordinary skilled in the art, at the time of the instant invention to transgenically produced antithrombin III comprising a monosaccharide composition by the method steps claimed in U.S. Patent No. 5,843,705.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antithrombin III having a specific glycosylation pattern and obtained from transgenic goat milk, does not reasonably provide enablement for any antithrombin III having any glycosylation differences and obtained from any transgenic mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is drawn to a transgenically produced antithrombin III comprising a monosaccharide composition wherein the antithrombin III is transgenically produced in a mammal.

The claims, as written, read on any animal model. However, the specification fails to provide any teachings or guidance with regard to the generation of any other animal model, other than a transgenic goat which would predictably produce the instantly claimed monosaccharide composition. The art of transgenics is not a predictable art with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species. The observation is further supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39, Summary. Cole et al

(1994) J. of Cellular Biochemistry Suppl.. Vol. 0 (18 D) p 265 disclose that NGNA and NANA acid were found on both therapeutic proteins (antithrombin III and LA-tPA), NGNA therefore appears to be a function of expressing the protein in goats. Given such species differences in the expression of a transgene, one of skill in the art would have been required to undergo undue experimentation to determine which promoter, enhancer, intron, exon, and transgene construct would produce the desired phenotype in any and all animals.

As a second issue, while the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic goat comprising antithrombin III transgene of interest wherein antithrombin III secreted by the goat milk has a specific glycosylation pattern inherent to the host species, it is not predictable that the broad glycosylation pattern of the expressed antithrombin III of the claimed invention would be produced by said goat.

The intention of the animal model, as defined in the specification of the instant application, is for transgenically producing antithrombin III in goats' milk comprising monosaccharides having a specific glycosylation pattern. The claims reads on any glycosylation pattern of antithrombin III that differs from that found in human plasma, but the specification only teaches specific glycosylation patterns of a goat produced antithrombin III. Given such a distinction in glycosylation pattern to host in the expression of antithrombin III, it would require undue experimentation to generate a general model that exhibits all the glycosylation pattern seen in any transgenic mammal or any glycosylation pattern of antithrombin III. It is standardly and well known in the art that glycosylation patterns are a function of the host cell in which the

protein product is translated and post-translationally modified by the host enzymes. There is insufficient objective evidence provided to indicate that the numerous embodiments of different glycosylation patterns now claimed would be predictably obtainable from a goat host or any other host. In Drohan review (1997), "The past, present, and future of transgenic bioreactors" disclosed that proteins have few postranslational modifications, mainly removal of the signal peptide and N-linked glycosylation. It appears that cleavage of signal peptides and the addition of carbohydrate chains at multiple sites to protein precursors in the mammary gland are performed adequately. Drohan further state that the carbohydrate composition and structure of transgenic proteins may differ from that of their human counterparts. Drohan continue further by disclosing the site-specific addition of oligomannose to specific asparagine residues of recombinant antithrombin III was also observed in the goat mammary gland. Drohan concludes that these species- and protein- specific glycosylation patterns may affect therapeutic efficacy, binding to cellular receptors and clearance of the recombinant proteins in patients. The specification is only enabling for a transgenic goat comprising monosaccharide compositions of GalNAc, Fus, GlcNAc, Gal, Man, and NANA/NGNA; having one of its glycosylation sites comprising oligomannose and/or hybrid oligosaccharide structures; primarily an oligomannose or hybrid type structure on one site and complex oligosaccharide on the remaining 3 sites; partially sialyated; sialic acid which includes NGNA; and a fucose on its proximal GlcNAc on each of the sites having complex oligosaccharides. The specification does not reasonably provide enablement for a general model, the applicants are limited to following: transgenic goat for the

production of antithrombin III comprising a monosaccharide composition of GalNAc, partially sialyated (NGNA), fucose on its proximal GlcNAc on each of the sites having complex oligosaccharide, and which lacks O-linked glycosylation, wherein the glycosylation sites comprising oligomannose and/or hybrid type structure on one site and complex oligosaccharide on the remaining 3 sites.

The claims are extremely broad, encompassing any and all animals and any glycosylation pattern of antithrombin III protein. The courts have stated that reasonable correlation must exist between scope of exclusive right to a patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). In view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to the production of transgenic animal models of more than one species, or all other glycosylation patterns of antithrombin III, the unpredictable state of the art with respect to the generation of transgenic any and all mammals, it would have required undue experimentation for one skilled in the art to make and/or use the claimed inventions as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,2,7,8 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1,2,7,8 and 11 are vague and indefinite in its recitation of " includes or including" because it does not define the metes and bounds of the encompassed monosaccharides of the claimed invention . It is suggested that applicant use a more accurate term such as "comprises or comprising" to overcome the objection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 5 is rejected under 35 U.S.C. 102(a) as being clearly anticipated by Edmunds et al (1994) J. of Cellular Biochemistry Suppl., Vol. 0 (18D) p. 265.

Edmunds et al disclosed a detailed oligosaccharide analysis of human plasma ATIII (tgATIII or transgenic antithrombin III) produced in the milk of transgenic goats and compared the glycosylation found to that of both human and goat plasma derived ATIII (pATIII). The

biantennary complex structures were found at 3 of the 4 glycosylation sites in tgATIII with the fourth site (Asn 155) containing High mannose/Hybrid structures (p. 265, U102). Thus, Edmunds et al clearly anticipate claim 5.

Claims 1, 4,6-7 and 10 are rejected under 35 U.S.C. 102 (a) as being clearly anticipated by Cole et al (1994) J. of Cellular Biochemistry Suppl.. Vol. 0 (18 D) p 265.

Cole et al teach the glycosylation patterns and the production of therapeutic proteins (antithrombin III) in the milk of transgenic animals (transgenic goat milk) can be achieved at very high expression levels compared to tissue culture. Cole et al further discloses the substitution of GalNAc for Gal due to the function of expressing the proteins in the mammary gland and not a species difference as goat plasma ATIII does not contain this substitution. The transgenic proteins are more fucosylated and less sialylated than their recombinant or plasma counterparts. NGNA and NANA acid were found on both therapeutic proteins, NGNA therefore appears to be a function of expressing the protein in goats. High mannose and/or hybrid structures were found on at least one site in each transgenic protein (p. 265, U100). Thus, Cole et al clearly anticipates claims 1, 4, 6-7 and 10.

Cole et al does not teach transgenically produced antithrombin III comprising a monosaccharide composition which includes: lacks O-linked glycosylation, GlcNAc monosaccharide composition, monosaccharide composition which is primarily an oligomannose or hybrid type structure on one site and complex oligosaccharide on the remaining 3 sites, fucose on its proximal GlcNAc on each of the sites having complex oligosaccharides, nor the transgenic

method for producing antithrombin III in a mammal. What Cole et al failed to disclose in his abstract are inherent to the claimed invention of the applicant for those encompassed characteristics of monosaccharide composition in relation to glycosylation patterns and/or positions of the monosaccharides.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Deborah Crouch

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